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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,341	05/03/2002	Michael R. Hayden	SMAR-0013	8795

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,341	HAYDEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2007 and 18 December 0207*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,37-40 and 42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/18/2007 has been entered.

Receipt is acknowledged of an amendment, filed 12/18/2007, in which claims 36 and 52-57 were canceled, and claims 35, 40, 43-50 were amended. Currently, claims 35, 37-40 and 42-51 are pending.

Any rejections and objections not reiterated in this action have been withdrawn.

Election/Restrictions

Applicant elected Group II and the disease hyperlipidemia with traverse in the reply filed on 9/23/2004. Currently, claims 35, 37-40 and 42-51 are under consideration.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35, 37-40 and 42-51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,814,962 (hereafter '962) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993, of record; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989, of record; see the entire reference). This rejection was made in the Office action mailed 10/26/2006 and has been rewritten to address the amendments to the claims in the reply filed 12/18/2007.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

In the instant case, claims 1-6 of the '962 patent recite methods of treating dyslipoproteinaemia, hypertriglyceridaemia, hypercholesterolaemia, hyperlipidaemia, familial hypertriglyceridaemia, and combined familial hyperlipidaemia and postprandial hyperlipidaemia comprising administering to the patient a defective recombinant adenovirus comprising a nucleic acid sequence coding for a biologically active human lipoprotein lipase (LPL). The claims of the '962 patent differ from the claims of the instant application in that they fail to disclose the use of a nucleic acid sequence encoding the S447X variant of human LPL.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2 legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the alignment mailed 11/19/2004, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of 2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

Therefore, it would have been obvious to modify the method of claims 1-6 of the '962 patent to include the S447X nucleic acid sequence taught by Kozaki et al because the claims recite the use of a nucleic acid encoding a biologically active human LPL and Kozaki et al teach that the S447X truncation is a functional LPL protein. One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity as taught by Kozaki et al.

Response to Arguments - Double Patenting

With respect to the rejection of claims 35, 37-40 and 42-51 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,814,962, Applicant's arguments filed 12/18/2007 have been fully considered but they are not persuasive.

The response asserts that the LPL S447X protein cannot inherently lower triglycerides and raise HDL-C. The response asserts that lowering triglyceride levels and increasing HDL-C is a surprising therapeutic benefit that can be achieved only if the protein is administered in an amount effective to achieve the result. Further, the response asserts that there is nothing in the art that suggest that viral gene therapy vectors could be used to administer an amount of protein that would be effective in this way, much less any basis for a reasonable expectation that viral vectors could be used to deliver an amount of S447X therapeutic that would have this effect. This is not found persuasive. Claims 2 and 5 of the '962 patent are specifically directed to the administration of a viral gene therapy vector to administer an amount of LPL protein that would be effective to reduce triglyceride levels in the patient. The specification of the '962 patent specifically teaches that decreased catalytic activity of lipoprotein lipase results in lower HDL-C levels and higher triglyceride levels (e.g., paragraph bridging columns 2-3). Thus, one would expect the administration of the viral gene therapy vector, as claimed in the '962 patent, to result in a decrease in triglycerides, as claimed, as well as an increase in HDL-C. Any LPL protein encoded by a viral vector that has about the same activity as the wild type LPL protein would be expected to have this property. Kozaki et al teach that the S447X truncation of LPL is a functional variant that has a specific activity twice that of wild type LPL. Accordingly, the

decrease in triglycerides and increase in HDL-C resulting from the expression of an LPL protein, including the S447X LPL protein, is not an unexpected result.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Arguments - 35 USC § 112

The rejection of claims 46 and 50 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 12/18/2007.

The rejection of claims 35-40, 42-45, 47-50 and 51 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 12/18/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35, 37-40 and 42-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al (WO 96/11276, of record; see the entire reference) in view of Kozaki et al (Journal of Lipid Research, Vol. 34, pages 1765-1772, 1993, of record; see the entire reference) as evidenced by Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989; see the

entire reference). This rejection was made in the Office action mailed 10/26/2006 and has been rewritten to address the amendments to the claims in the reply filed 12/18/2007.

Hayden et al teach the *in vivo* transduction of human cells with viral gene therapy vectors comprising the full-length LPL cDNA sequence for the treatment of hypertriglyceridemia (i.e. one form of hyperlipidemia) resulting from heterozygous or homozygous LPL deficiency (e.g. page 11, lines 10-31; page 12, lines 1-31). Hayden et al teach that decreased catalytic activity of lipoprotein lipase in humans results in lower HDL-C levels and higher triglyceride levels (e.g., page 2, lines 15-22; Example 1). Further, Hayden et al teach that gene therapy to introduce functional LPL may reduce the clinical manifestations stemming from hypertriglyceridemia (e.g., page 11, lines 10-16). Hayden et al teach the use of viral gene therapy vectors such as adenovirus (e.g., page 11, lines 10-16; page 12, lines 6-9 and 25-31).

Hayden et al do not teach the administration of a S447X LPL cDNA sequence.

Kozaki et al teach an expression vector comprising the S447X LPL cDNA sequence (e.g. Figure 2). Further, Kozaki et al demonstrate that the S447X LPL protein has a specific activity about twice as high as wild type LPL (e.g. Figures 3 and 4, LPL-446). Moreover, Kozaki et al suggest that the S447X mutation may have some protective effect against the development of hypertriglyceridemia (e.g. page 1771, left column, paragraph 1).

The S447X LPL nucleic acid taught by Kozaki et al necessarily encodes an LPL S447X RNA with at least 90% identity to nucleotides 256 through 1599 of SEQ ID NO: 4 and encodes a protein with at least 90% identity to SEQ ID NO: 3 and at least 95% identity to SEQ ID NO: 1. Kozaki et al disclose the primer sequences used to make the S447X truncation in the Figure 2 legend and cite Gotoda et al (Nucleic Acids Research, Vol. 17, No. 6, page 2351, 1989) as the

source of the human sequence (e.g. page 1766, Site-directed mutagenesis, see cited reference 22). As demonstrated in the alignment mailed 11/19/2004, the nucleic acid sequence disclosed by Gotoda et al is 100% identical to SEQ ID NO: 3. Because SEQ ID NO: 1 has a c-terminal truncation of 2 amino acids relative to SEQ ID NO: 3, the nucleic acid sequence disclosed by Gotoda et al is capable of producing an alignment with 100% identity over the entire length of SEQ ID NO: 1.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the adenoviral gene therapy vector of Hayden et al to include the S447X nucleic acid sequence taught by Kozaki et al in place of the wild type LPL sequence because Hayden et al teach it is within the ordinary skill in the art to use an LPL coding sequence in the adenoviral gene therapy vector for the treatment of hyperlipidemia associated with LPL deficiency and Kozaki et al teach that the S447X truncation is a functional LPL protein.

One would have been motivated to make such a modification in order to receive the expected benefit of increased LPL activity and a protective effect against the development of hypertriglyceridemia as taught by Kozaki et al. Since Hayden et al teach that decreased activity of LPL results in higher triglycerides and lower HDL-C, one would expect that increasing the LPL activity in a human would result in lower triglycerides and higher HDL-C. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 35, 37-40 and 42-51 under 35 U.S.C. 103(a) as being unpatentable over Hayden et al in view of Kozaki et al, as evidenced by Gotoda et al, Applicant's arguments filed 12/18/2007 have been fully considered but they are not persuasive.

The response asserts that the LPL S447X protein cannot inherently lower triglycerides and raise HDL-C. The response asserts that lowering triglyceride levels and increasing HDL-C is a surprising therapeutic benefit that can be achieved only if the protein is administered in an amount effective to achieve the result. Further, the response asserts that there is nothing in the art that suggest that viral gene therapy vectors could be used to administer an amount of protein that would be effective in this way, much less any basis for a reasonable expectation that viral vectors could be used to deliver an amount of S447X therapeutic that would have this effect. This is not found persuasive. Hayden et al teach the treatment of the clinical manifestations of hypertriglyceridemia in LPL deficiency (e.g., page 11, lines 10-16). Hayden et al teach that LPL deficiency results in increased triglycerides and decreased HDL-C (e.g., Abstract; page 2, lines 21-22). Thus, one would expect that increasing LPL activity would result in treating the hypertriglyceridemia (i.e., reducing triglyceride levels) associated with LPL deficiency, as well as increasing HDL-C levels. Any LPL protein encoded by a viral vector that has about the same activity as the wild type LPL protein would be expected to have this effect. Kozaki et al teach that the S447X truncation of LPL is a functional variant that has a specific activity twice that of wild type LPL. Accordingly, the decrease in triglycerides and increase in HDL-C resulting from the expression of an LPL protein, including the S447X LPL protein is not an unexpected result.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Daniel M Sullivan/
Primary Examiner, Art Unit 1636